UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/460,292	12/10/1999	David J. Mangelsdorf	UTSD:596	2313

7590 04/09/2003

Steven L. Highlander
FULBRIGHT & JAWORSKI LLP
600 Congress Avenue, Suite 2400
Austin, TX 78701

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	27

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/460,292	Mangelsdorf et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 21, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-14, 21, 23-27, 29, 44, and 45* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-14, 21, 23-27, 29, 44, and 45* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is an original application filed December 10, 1999, which claims benefit to provisional application 60/111,894, filed December 10, 1998.

Applicants' amendment filed January 21, 2003, paper number 26 has been received and entered. Claims 1, 2, 4-11, 21, 26, 27, 44 and 45 have been amended. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are pending and currently under examination.

Claim Objections

Claim 11 objected to because claim 11 recited "region of the LXRα**s**" is withdrawn. Amendment to the claim to recite "LXRα genes" has obviated the basis of the objection.

Information Disclosure Statement

It is noted that the specification has a large list of references listed (pages 82-97. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 10-14, 21, 23-27, 29, 44 and 45 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits hepatomegaly and cholesterol accumulation, does not reasonably provide enablement for transgenic mouse which comprises at least one endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants summarize the rejection and indicate that it appears that the scope of enablement rejection focuses on the breadth of the claims which encompass mutations outside the LXRα. gene. Applicants traverse without specific arguments and note the amendment to the claims to encompass the 'endogenous LXRα gene is "altered" in addition to being unable to respond to dietary cholesterol'. See Applicants' amendment, page 6, Section A. Applicants amendment has been fully considered but, and found persuasive in part.

Examiner agrees that the amendment to the claims to encompass alterations only to the endogenous LXRα gene obviates the basis of the rejection as it is drawn to affecting the LXRα allele by expression of other transgenes or knocking out of other endogenous genes. However, the claims still encompass the disruption of only one LXRα allele resulting the claimed phenotype. Previously, the claims encompassed a LXRα allele that could not express sufficient amounts of LXRα, encompassing either a disruption in the promoter or the open reading frame of the LXRα gene to reduce the amount of LXRα produced. The claims as amended further encompass the expression of altered forms of the LXRα which are not affected by cholesterol from the diet. As set forth in the basis of the previous rejection, claims 4-9 encompassing alterations in the LXRα coding region are not included in the basis of the rejection because a disruption in the LXRα allele that results in decreased levels of LXRα protein expression wherein the knock-out mouse is incapable of responding to dietary cholesterol is fully enabled. However, the claims encompass any mutation in the LXRα open reading frame which would result in the protein being produced but not having any activity. Further, the present claims do not indicate any specific nature of the alteration of the LXRα allele, only reciting a functional phenotype of the transgenic mouse. However, as noted in the basis of the previous rejection the instant specification only provides the necessary guidance for the disruption of the LXRα coding sequences. Further, Examiner would agree that various mutations or alterations of the LXRα coding sequence which result in a nonfunctional LXRα polypeptide wherein said animal lacks

the capacity to respond to dietary cholesterol would be obvious and enabled over the specific example disclosed in the working example in the instant specification, however, the specification fails to provide the necessary guidance to what those alteration would be besides the disruption of the open reading frame. The present application has defined a novel function for the LXRα *in vivo* using transgenic mice with a disrupted allele, however, the specification of the present application, nor the art of record, has resolved the many complexities of the role of this receptor in all animals, nor has it resolved the role of this molecule for use in full the scope recited in the claims. Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency, expression or affect of a particular alteration of a the LXRα gene or the expression of another transgene which may affect the LXRα gene. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), and this is particularly true in the field of transgenics and transgene behavior. Though the methodology of producing transgenic mice is becoming routine, the result of the genetic alteration can not be predicted.

With respect to transgenic mice consisting of only one affected LXRα allele, it would stand to reason that the remaining functional allele will be able to respond to circulating cholesterol. The only general evidence presented is that the founder LXRα(+/-) mice were normal. The specification provides no working evidence to asses whether the LXRα(+/-) mice would demonstrate a phenotype consistent with the phenotype recited and required by the claims. Further, with the ability to respond to dietary cholesterol the specification teaches that even LXRα(-/-) mice are capable of responding to dietary cholesterol at various levels of cholesterol

provided in the diet (page 68). Additionally, the limitation of the transgenic mouse being capable of responding to dietary cholesterol is very broad and non-limiting in that any transgenic mouse can respond to cholesterol. In the case of the LXRα(-/-) mice the response to higher amounts of cholesterol in the diet are ultimately cholesterol accumulation and hepatomegaly. These are the only two described phenotypes the specification sets forth for LXRα(-/-) mice and enables for use of said mice.

Finally, with respect to the method claims, these claims are included in the basis of the rejection because they require the generation and use of a transgenic mouse as encompassed by the broad independent claims. In particular, due to the unpredictability of transgene behavior and resulting animal phenotype, one of skill in the art would not know what cholesterol-related or bile acid-related phenotypes to monitor. Further, due to the unpredictability of transgene behavior, it is not clear that any transgenic mouse other that one having a disrupted LXRα coding sequence resulting in a null mutation or a nun-functional LXRα polypeptide would have a phenotype which could be consistent with that disclosed in the working examples and which could be used to study the effects on cholesterol or bile acid related metabolism.

Thus, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would have required undue experimentation by one of skill to practice the invention as claimed, and therefore, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Newly amended claims 1, 2, 21, 26, 27, 44 and 45 are unclear in the recitation of 'that responds to dietary cholesterol' because it is not clear if this is in reference tot the transgenic mouse as a whole, if this is specific limitation of the LXRα allele, or of the LXRα protein produced. Additionally, as set forth previously, the claims are indefinite because the metes and bounds of sufficient capacity and the levels of dietary cholesterol are not clearly defined in the claims or in light of the teachings of the present specification. First, the claims are unclear because the amount of cholesterol contemplated as being a dietary amount is not clearly set forth. In this case, the amount of cholesterol in circulation depends on consumption and cholesterol metabolism, and it is unclear if the claims encompass only normal levels or also encompass extremely low or extremely high levels of cholesterol. Second, with respect to a sufficient response to cholesterol, it is unclear what specific response or what level of response is contemplated. It is unclear if the response is only reflected in the LXRα gene expression and affect of an altered LXRα polypeptide, or to any possible response of any gene which can be measured. The specific "capacity" being measured is not clearly set forth therefore, the metes

and bounds of the claims are indefinite because what is encompassed by sufficient can not be fairly determined. Dependent claims 4-14, 23-25 and 29 are include in this rejection because they fail to clarify the basis of the rejection.

Applicants note the amendment to the claims and argue that there is no indefiniteness associated with the term as it is used and that the term encompasses any dietary cholesterol beyond that which is produced endogenously. See Applicants' amendment page 6, Section B. Applicants' arguments have been fully considered and found persuasive in part.

Examiner agrees that the term 'dietary cholesterol' is clear, however the limitation to whether it defines the mouse, allele or LXRα protein is not clearly set forth. Further, with respect to defining either the mouse, allele or LXRα protein, the specification teaches that the per cent amount of cholesterol in the diet is important in obtaining and observing the phenotype. The claim is unclear because the same transgenic mouse, provided a low cholesterol diet (0.2% cholesterol) would not have the recited phenotype because it could respond to the dietary cholesterol, however the same transgenic mouse on a high cholesterol diet would have the recited the recited phenotype. Amending the claim to encompass that said mouse exhibits hepatomegaly and cholesterol accumulation would obviate the basis of the rejection because it would clearly set forth the response to cholesterol in the diet.

Conclusion

No claim is allowed.

As noted in the previous office action, all the claims are free of the prior art of record because the prior art of record fails to teach or suggest the disruption the LXRα gene will result in an transgenic mouse with the observed phenotype. However, the claims are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630